REMARKS

Summary

Applicant presents new evidence, including Exhibits A and B, in support of its position that:

(1) the Furcht genestrip 11 is not a DNA collection device, but rather is an analysis device onto which a previously collected specimen is applied;

(2) the Furcht genestrip 11 device is not suitable for use as a DNA collection device due to its small size -- a functional requirement of the Furcht invention;

(3) pad 32 of the Furcht genestrip 11 is FTA-treated and therefore is not intended to be used, and would not be suitable, for rubbing against the skin of a person nor for insertion into the mouth of a subject for DNA specimen collection; and

(4) the Furcht genestrip 11 device would not be useful as a specimen collection device due to its intended fracturable structure.

The Applicant believes the new evidence and remarks show Furcht to be inappropriate for combination with Ricciardi et al. and Northview Biosciences, Inc., and traverse the rejection applied to claims 26-29, 32-36, 38 66 68-76 and 88-95.

Arguments

Applicant previously asserted that genestrip 11 of Furcht et al. did not posses one covered side thereby resulting in a failure of Furcht to meet all limitations of claims presently under examination. The Applicant believes that the new evidence and argument provided herein traverses the Examiner's rebuttal of the Applicant's previous

position. The Applicant regrets it did not detect this new evidence earlier whereby the extensive analysis and discussion by the both Applicant and the Examiner regarding the structure of genestrip 11 might have been avoided.

Genestrip 11 Is Not A DNA Collection Device And Could Not Be In View Of Its Size, Intended Function And Inclusion Of FTA Treatment.

Furcht et al teach, at Col 8, Lines 54-66 that genestrip 11 preferably has dimensions of 3.0 x0.5 x 0.1 cm and that collection pad 32 is an "FTA-treated collection pad 32." A strip measuring 3.0 x0.5 x 0.1 cm is show actual size below.

Genestrip 11 (*actual size*)

While mere variation in size or dimensions cannot confer patentability, Applicant argues that a strip of the genestrip 11 size or even twice its size would be impractical, if not impossible, for use as a DNA collection device in the field. Further, it would be impossible to use as a collection device within the mouth of a subject due to small size and the FTA-treatment applied to pad 32.

Typically, a device useful for buccal collection of saliva or epithelial cells would be approximately 6 inches long and have a sizable pad or absorbent structure attached thereto. Such a swab can be found in Ricciardi and such a swab is shown in Exhibit B -- *Whatman FTA and CloneSaver Cards* -- (attached hereto). Exhibit B presents a DNA Sponge Sampling Swab which is described as 5" to 6" in length and is intended for use with the Whatman FTA-treated cards. (Col 8, Lines 54-66). Thus, the actual size of a

DNA collection device is on the order of 5" to 6" to provide the user a device of sufficient size for practical use.

Further, the particular small size of the Furcht genestrip 11 is related to its functional utility within the Furcht device. Genestrip 11 is not a DNA collection device. Rather, it is designed to fit into the Furcht microelectromechanical system (MEMS) of Fig. 1. Furcht et al. describes the invention, in the Summary of the Invention (Col. 4, Lines 17-20) in the following terms:

> The present invention is a miniaturized thermal cycling device and an integrated, unitary microchip based detection device with microfluidic controls, on chip electronics.

Enlarging genestrip 11 to a useful size to function as a DNA collection device, and/or a buccal DNA collection device, would destroy its utility within invention of Furcht et al. which is that of a "microelectromechanical system" utilizing "microfluidic controls" structures to effect analysis.

Furcht et al. further support Applicant's contention that genestrip 11 is NOT a DNA collection device. Rather, it is an analysis component of the Furcht molecular genetic testing system 10 of Fig. 1 to which a previously collected specimen is applied:

> A critical operation in molecular genetic testing system 10 is specimen procurement (i.e., specimen collection and processing). The system 10 of the present invention employs a novel device, genestrip 11, which uses a chemically treated sample collection pad 32 (paper or synthetic material) onto which samples of biologic materials including blood, tissue samples or other sources of material containing either animal or microbial cells are added. (Col 8, Lines 34-41)(emphasis added).

This technique of adding a previously collected specimen to an FTA-treated sample holder, such as collection pad 32 of Furcht, is discussed in Exhibit A - *Whatman FTA Protocol BD03 - Applying and Preparing Buccal Cell Samples on FTA Cards for DNA Analysis* (hereinafter "Whatman FTA Protocol") at page 2. Under the heading "*Sample Collection and Application to FTA Cards*" the Whatman Protocol particularly specifies that an "Applicator" is used to collect the specimen from the subject and that the "Applicator" is then used to transfer the specimen onto the FTA-treated card. (See, Exhibit A, page 2).

Further, the FTA treatment on pad 32 of Furcht renders pad 32 unsuitable for rubbing against human skin and for direct insertion into the mouth of a subject and for collection of a buccal DNA sample therefrom. The Examiner's attention again is invited to Exhibit A -- *Whatman FTA Protocol* at page 2. The Whatman FTA Protocol teaches (See, highlighted portions) that FTA Cards are "impregnated with a patented chemical formula that lyses cell membranes and denatures proteins on contact." The Whatman FTA Protocol specifically warns against such mouth tissue contact by stating on page 2: "*Do not place the foam swab into the mouth after it has touch the FTA Card.*" Indeed, though the Whatman FTA Protocol does state on page 1 that the FTA Cards are non-toxic to humans, it nevertheless warns that a swab that has touched the FTA Card should not be placed in the mouth. Clearly, the FTA-treated pad 32 of Furcht should not be placed in the mouth or rubbed in the mouth to accomplish buccal DNA collection. Nor should a pad containing such cell destroying compounds be applied to human skin for the purpose of specimen collection.

Additional support may be found at page 2 under Protocol "Sample Collection and Application to FTA Cards." In this Protocol a swab is used to collect material from the mouth and to then apply the collected material to the FTA Card by rubbing the swab onto the FTA Card.

Therefore, the Applicant believes that the foregoing remarks support its contention that the genestrip 11 is not actually a DNA collection device that is used to contact a subject and acquire a specimen therefrom. Genestrip 11 is not used for this purpose and could not be used for this purpose due to its small size -- a functional requirement of the Furcht invention -- and the inclusion of the FTA treatment on pad 32 of genestrip 11 which should not contact a subject's tissues.

Finally, the Furcht genestrip 11 would not be useful as a specimen collection device due to its intended fracturable structure:

> The contents of the cocktail pouch 33 are released when the pressure sensitive membrane/valve 36 is ruptured. The cocktail pouch is ruptured by means of a sliding ferrule 37 affixed to a collar 38. The collar 38 slides over the transport tube 35 and over the cocktail pouch 33 when the Genestrip 11 is inserted into the genetic test card 14. This action pierces the cocktail pouch 33 and squeezes the contents of the cocktail pouch 33 downward through the pressure sensitive membrane/valve 36 and the tube 35. The contents of the cocktail pouch 33 then flow and immerse the FTA treated sample collection pad 32, thereby providing the complete biochemical reaction environment to perform the nucleic acid amplification. (Col 9, Lines 7-19).

Genestrip 11 contains a pressure sensitive membrane/valve 36 that is intended to be ruptured. Rupturing of this pressure sensitive valve releases the reagents on genestrip 11 and starts the reaction. The Applicant argues the such pressure sensitivity

militates against the rough use of genestrip 11 as a DNA collection device and the potential for release of the chemical reagents on the subject or in the subject's mouth is very undesirable.

Applicant believes these arguments remove Furcht as a reference for combination with Ricciardi and Northview Biosciences. Applicant respectfully requests that the rejection of claims 26-29, 32-36, 38 66 68-76 and 88-95 be withdrawn.

Remarks on Independent Claims Under Examination

In the Office Action at page 4, it is stated that Furcht teaches "a device for collecting material containing DNA that has a collection portion." The Applicant believes that this conclusion regarding Furcht has now been traversed and demonstrated to be incorrect as the Furcht device, due to its size, due to its intended use, and due to the inclusion of FTA treatment and intended fractureability could not serve as a suitable device for collecting DNA from a subject.

Collection of DNA from a subject is a limitation presented in all of the presently pending independent claims. Applicant believes the evidence presented in Exhibits A and B supports Applicant's position that: genestrip 11 is not such a collection device; the FTA-treated pad 32 of Furcht is not intended for direct application to the human body; and that the recommended protocol teaches the use of an applicator or swab to obtain a DNA sample from a subject followed by application of that sample onto an FTA treated paper such as that used in Furcht.

The Applicant further believes that the following passages from the independent

claims currently under examination support Applicant's position that a "collection device" is specifically identified in both the claim preamble and in the claim limitations of Applicant's claims and that such a "collection device" is not taught by Furcht.

26. "A device for selective collection from one of two adjacent surfaces of a body of a subject's body of material containing DNA comprising:

a device for collecting material containing DNA

"said rear surface having a covering thereon to prevent collection of material containing DNA..."

36. A device for collection of material containing DNA from the surface of the cheek within the mouth.

"Said rear surface having a covering thereon to prevent collection of material containing DNA from the tongue."

38. "A device for collection of material containing DNA from the surface of the tongue while avoiding collection of material containing DNA from the adjacent mouth tissue.

"Said rear surface having a covering thereon to prevent collection of material containing DNA from mouth tissues adjacent to the tongue..."

66. "A sample collection substrate for collection of DNA from a subject thereon."

"Said substrate having a second protective layer attached to a portion of said second side and second protective layer being foldable over said second side to prevent contamination of said second side..."

76. "A sample collection substrate for collection of DNA from a subject thereon."

"Said substrate having a protective layer on said first side..."

"A second protective layer for covering said substrate second side, said protective layer connecting with said first protective layer to form a protective pouch for holding said substrate prior to use."

86. A sample collection substrate for collection of DNA from a subject thereon, said substrate having a first side and a second side.

Substrate having a protective layer on said first side.

A second protective layer for covering said substrate second side.

Applicant also believes that claims 66,76, and 86 contain additional limitations directed to a second protective layer which render these claims distinct from the combination of Ricciardi, and Northview Bioscience and Furcht and which present a nonobvious, patentable distinction and which heretofore have not been considered or given patentable weight.

On page 5, first full paragraph, the Office Action states, "Furcht teaches buccal

scraping." Furcht does not teach buccal scrapping, at least insofar as genestrip 11 of the Furcht device is implicated. While buccal scrapping has long been known, the Furcht device could not be used for buccal scrapping due to its size which is limited by its intended purpose, and due to the fact that the pad 32 of Furcht is FTA-treated and should not be applied to the mouth of the subject.

Also, on page 5 of the Office Action, second full paragraph, it is stated that "Furcht teaches the use of FTA paper which inherently has some level of adhesion that is, at least, slightly variable in its binding." As shown in Applicant's remarks, the fact that the Furcht device includes FTA treatment on pad 32 militates against pad 32 being used to contact a human subject. Exhibit A advises that FTA treated cards or paper should not be applied to the subject, in particular a swab that has contacted an FTA-treated card should not be inserted into the subject's mouth. Therefore, Applicant believes that this statement on page 5 incorrectly suggests a use for the Furcht genestrip 11 since the Furcht pad 32 should not be used, due to the FTA treatment, as a collection device directly contacting the human subject.

In summary, the Applicant believes that the rejections are traversed as the combination of Furcht with Ricciardi, and with Northview Biosciences, Inc., fails due to the inapplicability of the Furcht device and the teachings of Furcht to the present invention which teaches a DNA collection device which is used directly against the skin and tissues of a subject in which use is contraindicated with respect to FTA-treated cards, papers or pads. (See, Exhibit A.)

The language cited by the Applicant with respect to each of claims 26, 36, 38, 66,

76, and 86 demonstrates that the limitations included in the claims require use of the claimed device in the actual collection of DNA from a subject. The Applicant has demonstrated that the Furcht device is not used, and is not intended to be used, in such a fashion, and therefore, the application of Furcht, in combination with the other cited art, is in apposite and the rejection should be withdrawn.

Therefore, the Applicant respectfully requests that claims 26-29, 32-36, 38, 66, 68-76, 78-86, and 88-95 be passed to issue in view of their allowability over the combination of Ricciardi, Furcht, and Northview Biosciences, Inc.

Respectfully submitted,

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Whatman FTA Protocol BD03

Applying and Preparing Buccal Cell Samples on FTA® Cards for DNA Analysis

FTA® Technology

FTA Cards are impregnated with a patented chemical formula that lyses cell membranes and denatures proteins on contact. Nucleic acids are physically entrapped, immobilised and stabilised for storage at room temperature. FTA Cards protect nucleic acids from nucleases, oxidation, UV damage and microbial and fungal attack. Infectious pathogens in samples applied to FTA Cards are rendered inactive on contact. Samples collected on FTA Cards and enclosed in a multi-barrier pouch can be shipped through the post making them an extremely useful tool for field collection of blood, plants or other specimens.

Indicating FTA Cards turn from pink to white on sample application and are recommended for clear or colourless samples. CloneSaver™ Cards are optimised for the room temperature collection and storage of plasmid DNA.

Handling Instructions

- Always wear gloves when handling FTA or CloneSaver Cards to avoid contamination of the Cards.
- Store unused FTA/CloneSaver Cards in a cool, dry place (void light and excessive humidity).
- Follow universal precautions when working with biological samples.
- FTA/CloneSaver Cards are non-toxic to humans.

Materials Required

- Whatman FTA Card – Indicating FTA Cards are recommended for use with clear samples. If applied to non-Indicating Cards, circle the application spot with a ballpoint pen or pencil.
- Whatman FTA purification reagent (cat no. WB120204).
- TE^{-1} buffer (10mM Tris-HCl, 0.1mM EDTA, pH 8.0).
- 1.2mm or 2.0mm diameter Harris micro punch or other paper punch.
- Whatman sterile foam tipped applicator (cat no. WB100032).
- Multi-barrier pouch (cat no. WB100010 – large, WB100011 – small).
- Desiccant pack for glycerol stock or high humidity storage areas (cat no. WB100003).
- Whatman FTA Protocol BD09 "Removing a Sample Disc from an FTA or CloneSaver Card for Analysis".

The FTA Principle – Get it Right First Time, Every Time

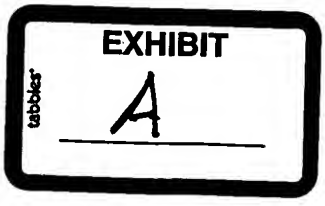
FTA works by lysis of cells releasing the nucleic acid within the matrix of the Card, where the nucleic acid will be entrapped among the cellulose fibres. Therefore the key step to ensure success is getting DNA-containing cells into the FTA in the presence of moisture to activate the cell-lytic and DNA-protective chemicals.

The processing of FTA works by washing away all cell debris and inhibitors of downstream analysis, leaving the DNA immobilised in the cellulose fibres. It is therefore essential that a good wash protocol is followed. Note: a good wash can be visualised in the processing of coloured samples such as blood and plants, where all of the red or green colour would have been removed from the punch. Insufficient washing can mean failure of your downstream analysis.

Controls

It is recommended that internal standard controls are used during each PCR analysis, these should include the following:

- Negative control.
- Negative control with washed, no-sample punch, to ensure that the punch does not cause a positive result.
- Positive control of a known DNA standard solution.
- Positive control standard added to a normally-washed, no-sample punch, to ensure that the punch does not inhibit the reaction.



Protocol

Sample Collection and Application to FTA Cards

1. Place the Indicating FTA Card on a clean, dry, flat surface. Label the FTA Card with a unique identifying name or number.
2. Remove one Foam Tipped Applicator from the protective packaging according to instructions on the packaging.
3. Holding the plastic handle of the Applicator, place the foam tip in the mouth and rub one side of the foam tip on the inside of the cheek for 30 seconds.
4. Repeat using the opposite side of the foam tip for the other cheek.
5. Run the foam tip along the gum-line and fold of the cheek and under the tongue, soaking up as much saliva as possible. Remove the Applicator from the mouth.
6. Carefully lift the paper cover of the Indicating FTA Card to expose the pink sample area. Press the flat, circular foam Applicator tip within the sample circle area. Without lifting the foam tip from the Card, roll the foam tip from edge-to-edge 3 times to completely saturate the sample area. Turn the Applicator over and repeat with the other side of the foam tip within the same circle. The sample area will turn white upon transfer of the sample.
7. Discard the Applicator according to laboratory procedure. Do not place the foam swab into the mouth after it has touched the FTA Card.
8. Allow the Card to dry for at least 1 hour at room temperature.
9. If the sample is to be archived, place in a multi-barrier pouch with desiccant or store in a humidity controlled, cool, dry environment.

If buccal cells are to be applied to more than one FTA sample area, use a new Applicator and repeat steps 1 – 9.

Preparing an FTA Disc for DNA Analysis

1. Take a sample disc from the dried spot following the instructions provided in the protocol entitled "Removing a Sample Disc from an FTA or CloneSaver Card for Analysis", protocol number BD09. For buccal samples a 2.0mm disc is recommended.
2. Place disc in PCR amplification tube.
3. Add 200µL of FTA Purification Reagent to PCR tube.
4. Incubate for 5 minutes at room temperature (the tube should be given moderate manual mixing to disrupt the debris and aid in washing).
5. Remove and discard all used FTA Purification Reagent using a pipette.
6. Repeat steps 3-6 twice, for a total of 3 washes with FTA Purification Reagent.
7. Add 200µL of TE^{-1} Buffer (10mM Tris-HCl, 0.1mM EDTA, pH 8.0).
8. Incubate for 5 minutes at room temperature.
9. Remove and discard all used TE^{-1} Buffer with a pipette.
10. Repeat steps 7-10 once for a total of 2 washes with TE^{-1} Buffer.
11. Ensure that all the liquid has been removed before performing analysis. The disk may be allowed to dry.

It is recommended that analysis be conducted within 3 hours of the disc washing. If this is not possible, the punch can be stored at 4°C or –20°C in a dark environment for up to 1 week.

DNA Analysis of Samples on FTA

PCR

- The washed and air-dried (optional) disc is now ready for analysis by PCR using standard protocols.
- The disc is included in the PCR reaction.
- There is no need to change reaction volume or PCR conditions due to the presence of the disc.
- For the PCR it can be safely assumed that the punch + DNA constitutes zero added volume.
- For PCR analysis of Genomic DNA on FTA a reaction volume between 25-50µL is recommended.

STR (Short Tandem Repeats)

- The washed and air-dried (optional) disc is now ready for STR analysis. A 1.2mm disc contains about 5-20ng DNA. Accordingly, an appropriate cycle number for this high quantity of DNA is 24 cycles, the amplification is performed directly in the MicroAmp tube.
- STR profiles have been successfully generated with 1.2mm FTA discs using kits from Applied BioSystems and Promega.

Technical Help

If you experience any problems with this protocol or wish to obtain additional information please contact Whatman Technical Service Team on the following regional numbers. Alternatively, please visit www.whatman.com for additional product information and further contact details.

North America 1-800-WHATMAN
Europe +44(0)1622 676670 – ask for technical service
Japan +81(0)3 2515 1242 – ask for technical service
Asia Pacific +65 6534 0138 – ask for technical service
China +86 21 6443 7176 – ask for technical service
India +91 22 529 7035 – ask for technical service

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